REMARKS

The Specification

The continuing data in the first paragraph of page 1 has been updated to provide the provisional application numbers that were assigned to Application Nos. 09/444,038 and 09/539,248 following conversion of these applications to provisional applications.

The specification was objected to because two paper copies of the sequence listing were submitted with the application as filed, and it was unclear to which one the statement of identical content referred. Applicant's undersigned attorney hereby states that the computer readable form (CRF) submitted at the time of filing is identical to the paper sequence listing labeled pp. 1-19.

The Claims

Claim 9 has been canceled; claims 1-6, 8, 10-14, 16, 17, and 20-29 have been amended; and new claims 31-42 have been added. Claims 4 and 30 were withdrawn from consideration by the Examiner. After entry of the above amendments, claims 1-8 and 10-42 will be pending in the application. To cover the cost of 11 addition claims (at $18 apiece), including 1 additional independent claim (at $84 apiece), the Office is hereby authorized to charge Applicant's deposit account no. 19-0134 in the amount of $282.

Claim Objections

Claims 2, 3, 6, 16, 17, 22, 27, and 28 were objected to as reciting an unelected invention (MuSK-R). All references to MuSK-R have been removed from the claims, thereby obviating this objection.

The Examiner indicated that claim 3 should recite SEQ ID Nos for the sequences designated EGFR1-I and EGFR1-II. Applicant has amended claim 3 so that it no longer recites these EGFR1 mutants. However, new claims 31-42 have been drafted so that EGFR1-I and EGFR1-II are recited according to SEQ ID NO. In particular, EGFR1-I is recited instead as "the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are

deleted" (see Example 1 (B) on page 26), and EGFR1-II is recited instead as "the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted" (see Example 1 (C) on page 27). See also Figure 1A.

Claim 16 was objected to as reciting two method steps in step (a). Claim 16 has been amended to break these out into separate steps.

The Examiner pointed out a redudancy in claim 27. Claim 27 has been accordingly amended.

The Examiner indicated that claims 9 and 10 were substantially duplicative. Without conceding the Examiner's position, Applicant has canceled claim 9, thereby obviating this objection.

Claim Rejections – 35 USC § 112, First Paragraph

Claims 1-3 and 5-29 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree with this rejection.

As Applicant understands it, the primary basis for this rejection is the alleged unpredictability of gene therapy. However, the claims are not directed to gene therapy, they are directed to a method of selecting genetically modified cells. More particularly, Applicant's invention revolves around the use of a particular type of mutated receptor as a selectable marker. The alleged unpredictability of gene therapy simply has nothing to do with the claimed invention.

The Examiner stated on page 5 of the Office Action that the nature of the invention is a method of producing genetically modified mammalian cells all of which express a mutated EGFR family member. The Examiner then stated that the cells so produced are disclosed solely as having use in gene therapy.

These statements are inapposite in at least two ways. First, the claims are not drawn to a method of *producing* genetically modified cells, but rather to *identifying* genetically modified cells, *i.e.* selection. Production and selection of genetically modified cells are not the same thing. More important than this distinction though is that regardless of whether the cells are "produced" or "identified," the use to which the genetically modified cells may later be put is of no moment. There are countless uses for a novel selection method, which is what Applicant's claimed invention is. Gene therapy certainly can involve selection, and Applicant's method may indeed be used as a step in a gene therapy protocol. However, the focus in the rejection on gene therapy misses the point.

As stated on the first page of the specification, the use of selectable markers is well known for the identification of prokaryotic and eukaryotic cells, and the use is essential because frequently when a DNA sequence of interest is introduced into a cell it will not necessarily lead to a phenotype that is readily determined. Other types of selectable markers include those that confer drug resistance (*e.g.*, G-418 and hygromycin) and selectable markers that are combined with fluorescence activated cell sorting (FACS), for example, green fluorescent protein (GFP). Alternatively, antibodies that recognize a cell surface molecule may be coupled to a fluorophore to help identify the cells of interest.

Applicant's claimed method should be viewed in light of this art, *i.e.* selection methodology, not gene therapy. The level of skill in this art is high. In view of what was known in the art and the guidance provided by the specification, the skilled artisan would have been able to practice the claimed method without undue experimentation.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections – 35 USC § 112, Second Paragraph

Claims 1-3, 6-15, 17, and 20-29 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Claim 1 was deemed vague and indefinite because the term "mammalian" was used in the preamble, but not in the body of the claim. Claim 1 has been amended to recite "mammalian" throughout, as have several dependent claims.

Claim 1 was deemed vague and indefinite in reciting "a modification to the intracellular and the extracellular domains." Claim 1 has been amended to change this recitation of "modification" to "modifications" as have several other claims containing the same language.

Claim 3 was deemed vague and indefinite in reciting "the sequences desigated EGFR1-I and EGFR1-II". As discussed above with regard to the claim objections, Applicant has amended claim 3 so that it no longer recites these EGFR1 mutants. However, new claims 31-42 have been drafted so that EGFR1-I and EGFR1-II are recited according to SEQ ID NO. In particular, EGFR1-I is recited instead as "the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are deleted" (see Example 1 (B) on page 26), and EGFR1-II is recited instead as "the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted" (see Example 1 (C) on page 27). See also Figure 1A.

Claims 17, 22, and 28 were rejected because of the phrase "preferably". These claims have been amended to remove this phrase.

Claim 20 was rejected because "immunoselection" was recited in the preamble, but there was allegedly no selection step recited in the body of the claim. Without conceding the Examiner's position, claim 20 has been amended to replace "immunoselection" in the preamble with "identifying".

Claim 23 and 24 were rejected as being vague and indefinite in reciting "derived from." Applicant respectfully traverses and submits that one of skill in the art of viral vectors would consider the term "derived from" neither vague nor indefinite in the context in which it is used in these claims. Page 15 clearly sets forth what is meant by vectors "derived from" certain viruses. However, in the interest of advancing prosecution, claims 23 and 24 have been amended to remove the phrase "derived from".

Claim 27 was rejected as being vague and indefinite because it was unclear whether both the protein of interest and the PTKR coding sequences were operatively linked to a single expression control sequence or if just or the other is operatively linked to it. Claim 27 has been amended to more clearly indicate that the protein of interest and the PTKR coding sequences are operatively linked to one or more expression control sequences; thus, claim 27 as amended covers either situation.

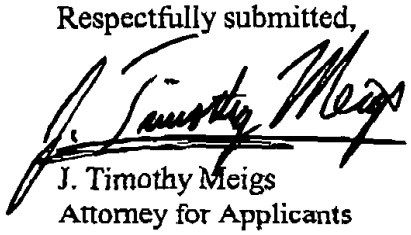
It is respectfully submitted that the amendments and remarks above overcome the rejections under 35 U.S.C. § 112, second paragraph, and Applicant therefore requests their withdrawal.

CONCLUSION

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

No new matter has been added. In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



J. Timothy Meigs
Attorney for Applicants
Registration No. 38,241

Genetic Therapy, Inc.
9 W. Watkins Mill Road
Gaithersburg, MD 20878
Telephone: 301-258-4715

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In The Specification

The paragraph on page 1, lines 3-11, which recites the continuing data, has been replaced with the following new paragraph:

-- This application claims the benefit under 35 USC §119(e) of the following United States provisional patent applications: (1) Provisional Application No. 60/166,594, filed November 19, 1999, for "Selectable Cell Surface Marker Genes;" (2) Provisional Application No. 60/304,204, [to be assigned,] filed November 19, 1999, [as Application No. 09/444,038] for "Selective Marker Genes," [and subject to a Petition for Conversion to Provisional Application, filed November 16, 2000;] and (3) Provisional Application No. 60/266,331, [to be assigned,] filed March 30, 2000 [as Application No. 09/539,248] for "Selectable Marker Genes[,]." [and subject to a Petition for Conversion to Provisional Application, filed November 16, 2000.] The disclosures of these three provisional applications are incorporated herein by reference in their entirety. --

In The Claims

Claim 9 has been canceled without prejudice or disclaimer.

Claims 1-6, 8, 10-14, 16, 17, and 20-29 have been amended as follows:

1. (Amended) A method of identifying genetically modified mammalian cells comprising the steps of:

a) introducing a nucleic acid sequence encoding a mutated protein-tyrosine kinase receptor (PTKR) operatively linked to an expression control sequence into a mammalian cell to form a genetically modified mammalian cell, wherein the mutated PTKR [either] comprises [a] modifications to the intracellular and the extracellular domains, comprises a modification to the extracellular domain, or excludes any nerve growth factor receptor(s) (NGFR) and comprises a modification to the intracellular domain;

b) allowing expression of the mutated PTKR in the genetically modified mammalian cell; and

c) identifying said genetically modified mammalian cell expressing the mutated PTKR.

2. (Amended) The method according to claim 1, wherein the mutated PTKR is [selected from] a mutated epidermal growth factor receptor (EGFR) [family member and muscle specific tyrosine kinase receptor (MuSK-R) family member].

3. (Amended) The method according to claim 2, wherein the mutated EGFR [family member] is a mutated EGFR1 [, optionally selected from the sequence designated EGFR1-I and EGFR1-II].

5. (Amended) The method according to [any preceding claims,] claim 1, wherein the mutated PTKR [is truncated from] comprises a deletion in the intracellular domain [, and optionally also from] or deletions in both the intracellular domain and the extracellular domain.

6. (Amended) The method according to claim 2, wherein the introducing step is accomplished by incorporating the nucleic acid sequence encoding the mutated EGFR [or MuSK-R] into a vector and introducing said vector into said mammalian cell.

8. (Amended) The method according to claim 1, wherein said identifying step is accomplished by contacting the genetically modified mammalian cells with an antibody that recognizes and binds to the mutated PTKR.

10. (Amended) The method according to claim 1, further comprising [the step of] separating the identified cells expressing the mutated PTKR.

11. (Amended) The method according to claim 1, wherein the mammalian cells are human cells.

12. (Amended) The method according to claim 11, wherein the human cells are selected from the group consisting of hematopoietic cells, liver cells, endothelial cells and smooth muscle cells.

13. (Amended) The method according to claim 11, wherein the human cells are hematopoietic cells.

14. (Amended) The method according to claim 13, wherein the [cells are] hematopoietic cells are stem cells or T-cells.

16. (Amended) A method of identifying genetically modified mammalian cells comprising the steps of:

a) incorporating into a vector a nucleic acid sequence encoding a mutated protein-tyrosine kinase receptor (PTKR) [family member], wherein said PTKR [either] comprises [a] modifications to the intracellular and the extracellular domains, comprises a modification to the extracellular domain, or excludes any nerve growth factor receptor(s) (NGFR) and comprises a modification to the intracellular domain;

b) introducing the vector into a mammalian cell to form a genetically modified mammalian cell;

c) [b)] allowing expression of the mutated PTKR in the genetically modified mammalian cell; and

d) [c)] identifying said genetically modified mammalian cell expressing the mutated PTKR.

17. (Amended) The method according to claim 16, wherein the mutated PTKR is [selected from] a mutated EGFR [, preferably EGFR1-I or EGFR1-II, and MuSK-R, preferably mMuSK-RI or mMuSK-RII].

20. (Amended) A method for [the immunoselection of] identifying transduced mammalian cells comprising: [,]

d) retrovirally transducing mammalian cells with a nucleic acid sequence encoding a protein-tyrosine kinase receptor (PTKR) [family member] operatively linked to an

expression control sequence; wherein said PTKR [either] comprises [a] modifications to the intracellular and the extracellular domains, comprises a modification to the extracellular domain, or excludes any nerve growth factor receptor(s) (NGFR) and comprises a modification to the intracellular domain;

e) incubating the transduced mammalian cells with a marked antibody which recognizes and binds specifically to the mutated PTKR; and

f) identifying the marked transduced mammalian cells.

21. (Amended) The method according to claim 20, wherein the mammalian cells are [human cells or] hematopoietic cells.

22. (Amended) The method according to claim 20, wherein the mutated PTKR is [selected from] a mutated EGFR [, preferably EGFR1-I or EGFR1-II, and MuSK-R, preferably mMuSK-RI or mMuSK-RII].

23. (Amended) The method according to claim 20, wherein the mammalian cells are transduced by a retroviral vector [derived] selected from the group consisting of a moloney murine leukemia viral vector, [virus (MoMLV),] a myeloproliferative sarcoma viral vector, [virus (MPSV),] a murine embryonic stem cell viral vector, [virus (MESV),] a murine stem cell viral vector, [virus (MSCV)] and a spleen focus forming viral vector, [virus (SFFV).]

24. (Amended) The method according to claim 20, wherein the mammalian cells are transduced by a lentiviral vector [derived from a lentivirus].

25. (Amended) The method according to claim 20, further comprising the step of separating the identified marked transduced mammalian cells from non-marked mammalian cells.

26. (Amended) The method according to claim 20, further comprising the step of expanding the marked transduced mammalian cells.

27. (Amended) A method of identifying mammalian cells expressing a protein of interest, comprising: [the steps of,]

a) introducing into a mammalian cell a nucleic acid [encoding a nucleic acid] comprising a DNA sequence encoding a protein of interest and comprising a DNA sequence encoding a protein-tyrosine kinase receptor (PTKR), wherein said DNA sequences are [family member] operatively linked to [an] one or more expression control sequences, wherein said PTKR [either] comprises [a] modifications to the intracellular and the extracellular domains, comprises a modification to the extracellular domain, or excludes any nerve growth factor receptor(s) (NGFR) and comprises a modification to the intracellular domain;

b) culturing the resulting mammalian cells; and

c) identifying mammalian cells which express the mutated PTKR thereby obtaining mammalian cells which express the protein of interest.

28. (Amended) The method according to claim 27, wherein the mutated PTKR is [selected from] a mutated EGFR [, preferably EGFR1-I or EGFR1-II, and MuSK-R, preferably mMuSK-RI or mMuSK-RII].

29. (Amended) The method according to claim 27, wherein the nucleic acid encoding the mutated PTKR and the nucleic acid encoding the protein of interest [in step (a)] are introduced [on] by a retroviral vector.

The following new claims 31-42 have been added:

31. (New) The method according to claim 3, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are deleted.

32. (New) The method according to claim 3, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted.

33. (New) The method according to claim 17, wherein the mutated EGFR is a mutated EGFR1.

34. (New) The method according to claim 33, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are deleted.

35. (New) The method according to claim 33, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted.

36. (New) The method according to claim 22, wherein the mutated EGFR is a mutated EGFR1.

37. (New) The method according to claim 36, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are deleted.

38. (New) The method according to claim 36, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted.

39. (New) The method according to claim 28, wherein the mutated EGFR is a mutated EGFR1.

40. (New) The method according to claim 39, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are deleted.

41. (New) The method according to claim 39, wherein the mutated EGFR1 comprises the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted.

42. (New) A method of identifying a genetically modified mammalian cell, comprising:

a) introducing a nucleic acid sequence encoding a mutated epidermal growth factor receptor 1 (EGFR1), operatively linked to an expression control sequence, into a mammalian cell to form a genetically modified mammalian cell, wherein the mutated EGFR1 either comprises: i) the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 679-1210 are deleted, or ii) the amino acid sequence set forth in SEQ ID NO:2 except that amino acid residues 25-312 and 679-1210 are deleted;

b) allowing expression of the mutated EGFR1 in the genetically modified mammalian cell; and

c) identifying said genetically modified mammalian cell expressing the mutated EGFR1.